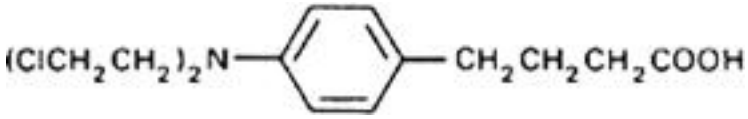
Chlorambucil (Chlorambucilum)

Molecular formula. $C_{14}H_{19}Cl_2NO_2$

Relative molecular mass. 304.2

Graphic formula.



Chemical name. 4-[*p*-[Bis(2-chloroethyl)amino]phenyl]butyric acid; 4-[bis(2-chloroethyl)amino]benzenebutanoic acid; CAS Reg. No. 305-03-3.

Description. A white or almost white, crystalline or slightly granular powder.

Solubility. Practically insoluble in water; freely soluble in ethanol (~750 g/l) TS and acetone R.

Category. Cytotoxic drug.

Storage. Chlorambucil should be kept in a well-closed container, protected from light.

Additional information. CAUTION: Chlorambucil must be handled with care, avoiding contact with the skin and inhalation of airborne particles.

Requirements

Definition. Chlorambucil contains not less than 98.0% and not more than 101.0% of $C_{14}H_{19}Cl_2NO_2$, calculated with reference to the anhydrous substance.

Identity tests

A. Place 20 mg in a test-tube, add 0.20 mL of potassium dichromate TS2, cover the tube with a piece of filter-paper moistened with sodium nitroprusside (8.5 g/l) TS and 0.05 mL of piperidine R. Heat the tube over a small flame; a blue spot appears on the filter-paper.

B. Dissolve 0.05 g in 5 mL of acetone R, and dilute with water to 10 mL. Add 0.05 mL of sulfuric acid (~100 g/l) TS, then add 0.20 mL of silver nitrate (0.1 mol/l) VS; no opalescence is observed immediately (absence of chloride ion). Warm the solution on a water-bath; an opalescence develops (presence of ionizable chlorine).

C. Mix 0.4 g with 10 mL of hydrochloric acid (~70 g/l) TS and allow to stand for 30 minutes, shaking occasionally. Filter, wash the residue with 2 quantities, each of 10 mL of water, and dry at ambient temperature under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R for 3 hours; melting temperature, about 146°C.

Melting range. 64-69 °C.

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.5 g of the substance; the water content is not more than 5.0 mg/g.

Related substance. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R2 as the coating substance and allowing the coated plate to dry at room temperature for 24 hours. Use as the mobile phase a mixture of 8 volumes of toluene R, 5 volumes of methanol R, 4 volumes of heptane R, and 4 volumes of ethylmethylketone R. Apply separately to the plate 10 µl of each of 2 solutions in acetone R containing (A) 20 mg of the test substance per mL and (B) 0.40 mg of the test substance per mL. After removing the plate from the chromatographic chamber, allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm). Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B.

Assay. Dissolve about 0.2 g, accurately weighed, in 10 mL of acetone R, add 10 mL of water, and titrate with carbonate-free sodium hydroxide (0.1 mol/l) VS using phenolphthalein/ethanol TS as indicator. Repeat the operation without the substance being examined and make any necessary corrections. Each mL of carbonate-free sodium hydroxide (0.1 mol/l) VS is equivalent to 30.42 mg of $C_{14}H_{19}Cl_2NO_2$.